Thrombotic Microangiopathy: An Under-Recognized Cause of CKD Following Viper Envenomation

To the Editor: There is only minimal literature on thrombotic microangiopathy (TMA) as a cause of acute kidney injury following envenomation.[1] We present a series of 7 cases with kidney failure following envenomation, with biopsy result consistent with TMA (Supplementary Methods and Supplementary Image S3). The clinical and histologic findings are given in Table 1. Despite absence of cortical necrosis, 4 patients did not recover and 3 had incomplete recovery.

Following envenomation, the initial event is venom-induced coagulopathy, which resolves by 48 hours. A small subset develop TMA—characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction, evolving over 3 to 6 days post-envenomation.[2] It is unknown whether all patients who fulfill the hematologic criteria for TMA develop consistent renal lesions of TMA. So far, only 30 studies (including 15 necropsies) reported renal histologic lesions of TMA following envenomation; most of the cases had cortical necrosis.[3] Hematologic TMA is associated with severe forms of acute kidney injury and longer time on dialysis.[3] Despite the strong association between TMA and acute kidney injury, it is reported that 80% to 95% with hematologic evidence of TMA eventually become dialysis independent.[3] However, there is only minimal literature on the long-term outcomes of these patients. An Indian study reported nonrecovery of kidney function in 2 patients with TMA and cortical necrosis.[4] Evidence of renal TMA might be overlooked under light microscopy; the milder variants may have only acute tubular necrosis and the severe cases demonstrating cortical necrosis. Date *et al.*[4] reported that kidney biopsies revealing acute tubular necrosis under light microscopy demonstrated fibrin thrombi by electron microscopy.[5]

The reported prevalence of chronic kidney disease following hemotoxic envenomation varies from 16% to 41%.[S1,S2] TMA might likely be responsible for the nonrecovery of kidney function in a few. To the best of our knowledge, this is the first to report the long-term outcomes in patients with biopsy evidence of TMA.

Table 1. Clinical, biochemical, and histologic characteristics

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (yr)	30	38	40	46	44	54	45
Sex	Female	Female	Female	Female	Female	Female	Male
Envenomation and acute kidney injury gap	<24 h	10 d	48 h	<24 h	<24 h	5 days	<24 h
Admission creatinine (mg/dl)	4.2	9.35	4.07	4.01	5.9	4.81	6.62
Hemoglobin (g/dl)	10.7	10.8	8.6	10.5	9.3	8.1	7.6
Platelet count at presentation (cells/mm^3)	88 × 10^3	298 × 10^3	11 × 10^3	90 × 10^3	75 × 10^3	229 × 10^3	21 × 10^3
WBCT at admission	>20 min	Normal[a]	>20 min	>20 min	>20 min	Normal[a]	20 min
Peripheral smear	Schistocytes with reduced platelets	Late presentation	Schistocytes with reduced platelets	Schistocytes with reduced platelets	Schistocytes with reduced platelets	Normal platelet counts; 1% schistocytosis	Schistocytes with reduced platelets
Dialysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shock	Yes	No	No	No	No	No	No
Resolution of coagulopathy	7 d	Delayed presentation	7 d	6 d	9 d	5 d	6 d
Envenomation to biopsy time	25 d	22 d	30 d	30 d	30 d	28 d	25 d
Kidney biopsy—glomeruli	19 glom, 3 partial sclerosis; mesangiolysis in remaining ones. Fibrin thrombi in 1	12 glom, 4 with ischemic wrinkling. Mesangiolysis, mild mesangial proliferation.	15 glom; 4 have mesangiolysis and ischemic wrinkling. Fibrin in mesangium.	14 glom; 2 sclerosed. Fibrin deposition, subendothelial widening, and irregular GBM thickening in 3 glomeruli.	5 glom: mesangiolysis, subendothelial widening, capillary basement membrane duplication and fibrin thrombi.	17 glom; 2 sclerosed. Mesangiolysis, subendothelial widening, capillary basement membrane duplication, and fibrin thrombi	17 glom; subendothelial widening and irregular GBM thickening in 5

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Table 1. (Continued) Clinical, biochemical, and histologic characteristics

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Tubules	RBC, eosinophilic casts with 40% ATN; 30% tubular atrophy	Dilated tubules, eosinophilic, RBC and few neutrophilic casts with mild ATN (25%)	30% ATN with eosinophilic and granular casts. Tubular atrophy 30%	60% ATN with reddish granular casts.	ATN (50%) with RBC cast	ATN (40%)	ATN (40%), with RBC and neutrophil cast
Interstitium	Few infiltrates of lymphocytes and neutrophils	Inflammation in (20%) of core; lymphocytes, few eosinophils and neutrophils	Patchy interstitial inflammation comprised of lymphocytes	Edematous; few lymphocytes	Edematous with myxoid change	Edema and myxoid change in 30% of core; lymphocyte and histiocyte infiltration in 20%.	Edema and myxoid change 20% of core; lymphocyte, histiocyte, few neutrophil infiltration in 20%.
Vessels	Fibrinoid necrosis	Medial hyperplasia	Intimal thickening	Medial hypertrophy and fibrin thrombi in smaller vessels	Intimal thickening	Medial hypertrophy, intimal fibrosis, and narrowing of the lumen; onion skinning and nuclear fragmentation.	Medial hypertrophy
Immunofluorescence	Negative	Mesangium IgG and C1q 1+ (nonspecific)	Negative	IgM 1+ mesangium (nonspecific)	Negative	Negative	Negative
Outcome	Dialysis dependent	Dialysis dependent	Dialysis independent; restarted dialysis after 4 yr	eGFR 34 ml/min per 1.73 m^2 after 12 mo	eGFR 37 ml/min per 1.73 m^2 after 5 mo	Dialysis dependent	Dialysis dependent

AKI, acute kidney injury; ATN, acute tubular necrosis; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; Glom, glomerular; RBC, red blood cell; WBCT, whole blood clotting time.
[a]Envemomation managed elsewhere, referred for management of kidney failure. Both have clotting times >20 minutes documented from the referring center. Rest of hematologic workup not available.

Prospective studies are required to delineate the pathogenic mechanisms and susceptibility factors of venom-induced TMA. The long-term sequelae of biopsy-proven TMA seem poor, with most severe cases not recovering kidney function. More research is needed to look into the utility of therapeutic options, such as plasmaphereses.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Materials and Methods.

Supplementary References.

Supplementary Images.

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